ATTORNEY DOCKET NO. 018743/0276322

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	High *et al.*	Art Unit:	1636
Serial No.:	09/393,844	Examiner:	Sullivan, DM.
Filed:	September 10, 1999		
Title:	METHODS AND COMPOSITIONS FOR USE IN GENE THERAPY FOR TREATMENT OF HEMOPHILIA		

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 C.F.R. §1.131

Dear Sirs:

I, Dr. Roland W. Herzog, do hereby declare and state that:

1. I am a co-inventor of the subject matter described and claimed in United States Patent Application Serial No. 09/393,844, filed September 10, 1999, entitled: "METHODS AND COMPOSITIONS FOR USE IN GENE THERAPY FOR TREATMENT OF HEMOPHILIA".

2. I am familiar with the prosecution history of Application Serial No. 09/038,910.

3. I understand that the Examiner has cited Wilson *et al.* (U.S. Patent No. 5,866,552) under 35 U.S.C. §102(e) against the claims of Application Serial No. 09/393,844.

4. I submit that Wilson *et al.* (U.S. Patent No. 5,866,552) is not available as prior art under either of 35 U.S.C. §§102 and 103.

5. Prior to the filing date of Wilson *et al.*, the recombinant AAV vector including DNA encoding Factor IX was first constructed at the Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

6. We were diligent from the time of conception of the invention with respect to the recombinant Factor IX AAV vector, reducing to practice the recombinant Factor IX AAV vector, and up until the time of filing the patent application.

7. Evidence of the conception and reduction to practice of the present invention is supplied in the form of a copy of four pages from laboratory notebooks (Exhibit A), each of which is labeled 1 to 4, prior to September 6, 1996, the filing date of Wilson *et al.* The first three pages of Exhibit A are additional evidence of reduction to practice of recombinant Factor IX AAV vector. The fourth page of Exhibit A was previously submitted with the two Declarations under 37 C.F.R. §1.131 of record (submitted on May 18, 2004, and on June 5, 2001).

8. In particular, pSSV9 vector was used to make the Factor IX AAV vector (see Exhibit A, pages 1-3). pSSV9, also referred to as PSSV and psub201, is an AAV vector that contains two inverted terminal repeats flanking an Xba I site, as evidenced by accompanying Exhibits B and C, publications by Lai et al. (*Genetic Vaccines and Therapy* 2:1 (2004)) and Miao et al. *(J. Virol.* 74:3793 (2000)), respectively. For example, in Exhibit B, page 2 (Methods, Virus preparation), vector construction is described as follows: "[t]his cassette was inserted between the inverted terminal repeats of the serotype 2 rAAV plasmid pSSV9....achieved by blunt end ligation of the 3800 bp CMV.RPE65 cassette with the large fragment of pSSV9 following Xba I digestion" In Exhibit C, page 3794 (Materials and Methods), rAAV vector is indicated to have been prepared as follows: "[p]reparation and characterization of rAAV-FIX from pSSV9-MFG-hFIX." Exhibits B and C therefore corroborate that pSSV9, used to produce

recombinant Factor IX vector, is an AAV vector which includes two inverted terminal repeats.

9. FIX intron 1 and a promoter/regulatory sequence was present in the recombinant Factor IX AAV vector, as indicated on Exhibit A, page 3, lines 1 and 10 ("pCEP-FIX intron"). As indicated on Exhibit A, page 3 (approximately lines 20-23), a 4 kb fragment was purified from Sal I digested/T4 polymerase treated "pCEP-FIX intron" for insertion into Xba I digested/T4 polymerase treated pSSV9. The 4 kb fragment includes, *inter alia*, a promoter/regulatory sequence, a 1.4 kb portion of intron 1 (*i.e.*, from about 0.3 kb to about 1.7 kb in length) and FIX cDNA.

10. A diagram of the complete recombinant Factor IX AAV vector, including the cytomegalovirus immediate early promoter/enhancer, abbreviated "CMV", is illustrated on Exhibit A, page 4, as pSSV-F.IX intron.

11. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10-25-05

Roland W. Herzog, Ph.D.

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PATENT
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Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 C.F.R. §1.131

Dear Sirs:

I, Dr. Katherine High, do hereby declare and state that:

1. I am a co-inventor of the subject matter described and claimed in United States Patent Application Serial No. 09/393,844, filed September 10, 1999, entitled: "METHODS AND COMPOSITIONS FOR USE IN GENE THERAPY FOR TREATMENT OF HEMOPHILIA".

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4. I submit that Wilson *et al.* (U.S. Patent No. 5,866,552) is not available as prior art under either of 35 U.S.C. §§102 and 103.

5. We were diligent from the time that we conceived the invention with respect to the recombinant Factor IX AAV vector, reduced to practice the recombinant Factor IX AAV vector I, and up until the time of filing the patent application.

6. Evidence of the conception and reduction to practice of the present invention is supplied in the form of a copy of four pages from our laboratory notebooks (Exhibit A), each of which is labeled 1 to 4, prior to September 6, 1996, the filing date of Wilson *et al.* The first three pages of Exhibit A are additional evidence of reduction to practice of recombinant Factor IX AAV vector. The fourth page of Exhibit A was previously submitted with the two Declarations under 37 C.F.R. §1.131 of record (submitted on May 18, 2004, and on June 5, 2001).

7. In particular, pSSV9 vector was used to make the Factor IX AAV vector (see Exhibit A, pages 1-3). pSSV9, also referred to as PSSV and psub201, is an AAV vector that contains two inverted terminal repeats flanking an Xba I site, as evidenced by accompanying Exhibits B and C, publications by Lai et al. (*Genetic Vaccines and Therapy* 2:1 (2004)) and Miao et al. *(J. Virol.* 74:3793 (2000)), respectively. For example, in Exhibit B, page 2 (Methods, Virus preparation), vector construction is described as follows: "[t]his cassette was inserted between the inverted terminal repeats of the serotype 2 rAAV plasmid pSSV9....achieved by blunt end ligation of the 3800 bp CMV.RPE65 cassette with the large fragment of pSSV9 following Xba I digestion" In Exhibit C, page 3794 (Materials and Methods), rAAV vector is indicated to have been prepared as follows: "[p]reparation and characterization of rAAV-FIX from pSSV9-MFG-hFIX." Exhibits B and C therefore corroborate that pSSV9, used to produce recombinant Factor IX vector, is an AAV vector which includes two inverted terminal repeats.

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Date: 10/25/05

Katherine A. High, M.D.